

## LETTERS TO THE EDITOR

**Effects of Physiologic and Pharmacologic  
Adrenergic Stimulation on Heart  
Rate Variability**

The report by Ahmed et al. (1) in a recent issue of the Journal examines the influence of exogenous beta-sympathomimetic agents, postural stress and exercise on time and frequency domain measures of heart rate variability, presumably as a model to explain the heart rate variability observed in disease states that are characterized by increased sympathetic drive. Several points regarding this report require reconsideration.

The results reported concerning the effect of isoproterenol on heart rate variability differ markedly from those noted by Binkley et al. (2) in a similar group of subjects but with lower doses of isoproterenol. In that report, a marked increase in low frequency heart rate variability was observed, and there was little change in the high frequency variability. A recent editorial by Malik and Camm (3) points to an important mechanism that may account for these differences that was not discussed by Ahmed et al. As Malik and Camm note, extremes of stimulation of the sinus node such that it is effectively "saturated" and thus maximally stimulated do not permit the superimposition of variability on the resultant extremes of heart rate. Indeed, isoproterenol in the report by Ahmed et al. produced the greatest increase in heart rate of any of the maneuvers, and the above mechanism most likely accounts for the observed decrease in both low and high frequency heart rate variability and the difference between these data and those of Binkley et al., in which a much lower stimulating dose of isoproterenol was used. Exercise, that produced the second highest increase in heart rate in the Ahmed et al. study, had a similar effect, most likely due to the same mechanism. Thus, as the report by Binkley et al., as well as others, has shown, low frequency heart rate variability can reflect beta-sympathomimetic stimulation but within recognized extremes of stimulation, as noted by Malik and Camm. It is not therefore so much the difference in exogenous versus endogenous neural stimulation that accounts for these effects, but the magnitude of stimulation. Conversely, the absence of change in heart rate variability with administration of beta-blockade indicates that these subjects had little rest sympathetic tone under the study conditions. This is corroborated by the lack of change in heart rate with administration of the beta-blocker.

The supposition that administration of substances such as epinephrine mimic the environment encountered in congestive heart failure and thus lend insight into the heart rate variability observed in this condition is erroneous. Although epinephrine may be increased to some extent in congestive heart failure, it is norepinephrine, rather than epinephrine, that has pathophysiologic activity in this condition. This increase in norepinephrine is in fact an epiphenomenon resulting from the "spillover" of this neurotransmitter, which follows from the greatly enhanced sympathetic drive of this patient group. Accordingly, it is not the influence of circulating norepinephrine that accounts for the observed changes in heart rate variability, but the direct effect of augmented sympathetic nerve traffic, reflected by the increase in circulating norepinephrine, that produces these changes. Indeed, the intervention in the Ahmed et al. study that most closely simulates the sympathetic activation encountered in congestive heart failure was postural stress, which produced changes in low and high frequency

variability, which would be expected under conditions of increased sympathetic drive and reduced parasympathetic tone noted in patients with congestive heart failure.

To state that these data force a reconsideration of the conclusions stated in previous studies is to ignore the extensive work preceding the report by Ahmed et al. that demonstrates the limitations as well as the strengths of this methodology and that has been well recognized and stated by careful investigators in this area of research. Binkley et al. (2), as well as numerous other investigators, have confirmed that parasympathetic blockade alters low as well as high frequency variability. This dual control of low frequency variability was offered as a possible explanation for the absence of change in low frequency heart rate variability with chronic angiotensin-converting enzyme inhibition in patients with congestive heart failure (4). It was speculated that decreases in sympathetic drive with angiotensin-converting enzyme inhibition were offset by concomitant increases in parasympathetic tone, resulting in the absence of any net change in low frequency variability (4). Similarly, the "alternative explanation" offered by Ahmed et al. for previously reported changes in heart rate variability in response to angiotensin-converting enzyme inhibition are not tenable and in fact highlight the advantages of analyzing heart rate variability in the frequency rather than the time domain. In the time domain, one cannot distinguish whether the changes in total heart rate variability are due to the reported inverse relation between sympathetic activation and total heart rate variability (5) or to a specific augmentation of parasympathetic tone. However, the report by Binkley et al. clearly showed that the increase in total heart rate variability is entirely due to an increase in the high frequency component, and there is nothing in the report by Ahmed et al. or in previous investigations to indicate that high frequency heart rate variability is governed by any mechanism other than parasympathetic control.

Therefore, the observations reported by Ahmed et al. do not truly vary from those that could be predicted on the basis of the work of several investigators whose efforts have been fundamental to the development of these methods (6). The data of Ahmed et al. provide intriguing observations regarding the influence of exogenous stimuli of differing pharmacologic properties on heart rate variability but do not provide a valid model of disease states for the reasons noted previously. Accordingly, these data serve as an example of the challenging insights into the physiologic and pathophysiologic mechanisms that may be elucidated by this system of analysis rather than discouraging the use of what has been and will continue to be a valuable tool for clinical investigation.

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### Reply

Binkley raises important issues regarding our study on the effects of physiologic and pharmacologic adrenergic stimulation on heart rate variability that merit further clarification. He correctly points out that our findings with isoproterenol differ from those previously reported by his group (1). His explanation for the discrepancy is probably correct because we repeated isoproterenol stimulation in normal subjects at a dose of 25 ng/kg body weight per min and showed that there is indeed an increase in low frequency power at the lower dose of stimulation. As Binkley points out, these findings are consistent with the mechanism proposed by Malik and Camm (2), which states that there is a decrease in heart rate variability with intense stimulation. We believe that our data regarding both sympathetic stimulation (3) and parasympathetic stimulation (4) support this hypothesis. However, the implications of this hypothesis are quite dramatic and may be applicable to other data of Binkley et al. as well. If a heart rate variability variable is considered a measure of autonomic tone, then it should increase monotonically as autonomic tone increases. However, the possibility that intense stimulation may be associated with a low heart rate variability value, as proposed by Malik and Camm, implies that both low and high levels of autonomic tone may be associated with a low heart rate variability. Binkley notes that in his study of congestive heart failure, there was a "greatly enhanced sympathetic drive." On the basis of the mechanism of Malik and Camm, how can we be sure that a low value for any variable of heart rate variability in this situation reflects anything but intense sympathetic stimulation? Furthermore, Binkley notes incorrectly that there are no data in our study to suggest that high frequency power is governed by any mechanism other than parasympathetic control. In fact, sympathetic stimulation was associated with a decrease in high frequency power for some conditions. Other investigators (5) have also noted a decrease in the high frequency component with sympathetic stimulation. Thus, treatment with an angiotensin-converting enzyme inhibitor, which may diminish the sympathetic drive in these patients, may thereby result in an increase in heart rate variability, perhaps even the high frequency power. This alternative hypothesis certainly does not negate the possibility that there is also an increase in parasympathetic tone.

Another important issue raised by Binkley is whether there is a difference in the heart rate variability response to pharmacologic beta-adrenergic stimulation versus endogenous neural stimulation.

Clearly, in the current study (3) only upright tilt was associated with an increase in the low frequency power, suggesting that this maneuver results in different effects on heart rate variability from those observed with pharmacologic beta-adrenergic stimulation. We further tested this hypothesis by removing the confounding influence of parasympathetic tone (6). Upright tilt after atropine administration was associated with a significant increase in the low frequency power, whereas isoproterenol (given at a dose [25 ng/kg body weight per min] that resulted in an increase in low frequency power in the absence of atropine) did not increase the low frequency power (6). It therefore appears that the heart rate variability response to sympathetic stimulation does depend on the type of stimulation.

Finally, although in congestive heart failure the increase in sympathetic tone may be predominantly neurally mediated, there are a variety of physiologic states that are associated predominantly with an epinephrine response or a mixed epinephrine/norepinephrine response (7). Thus, it may be important to understand the effects of circulating catecholamines on heart rate variability.

In summary, our findings highlight the observation made by Malik and Camm (2) that "the idea that in all different circumstances, the heart rate variability components closely reflect the degree of autonomic tone has no solid basis." However, there is clearly important information that can be gleaned from heart rate variability analysis. It is the challenge for the future to develop a better physiologic model that will allow us to use these techniques to better evaluate changes in autonomic tone.

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